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**ROBUST SUMMARIES and
SIDS DOSSIER for:
2-Ethylhexanoic Acid**

.....

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

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SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$ \begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}-\text{C}-\text{OH} \\ \\ \text{CH}_2\text{-CH}_3 \end{array} $
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5							
	Info. Available	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degradability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5							
	Info Available	OECD Summary	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

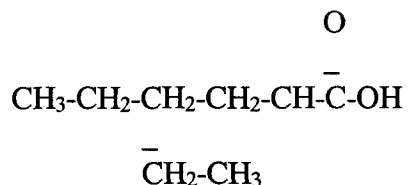
2.3 Common Synonyms:

α -Ethylcaproic acid
2-Ethylcaproic acid
 α -Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**



* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **Physical-Chemical Data**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES []
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES []
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES ☐
NO ☒

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water (Preferred Study)**

log Pow = 3 at 25°C

Method: calculated ☒
 measured ☐

GLP: YES ☐
 NO ☒

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated ☒
 measured ☐

GLP: YES ☐
 NO ☒

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES ☐
NO ☒

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup ☐ open cup ☒

Method:

GLP: YES ☐
NO ☒

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES ☐
NO ☒

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 pH in Water

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES ☐

NO ☒

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 Other Data

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 Source of Exposure

- * 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

- 4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

- * 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

- 4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 Other Remarks:

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 Environmental Fate and Pathways

* 5.1 Degradability (Biotic and Abiotic)

5.1.1 Biodegradability

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic []

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, I. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES []
NO [X]

Test Results: BOD₅ = 60 % of Theoretical (2.44 g O₂/g test substance).
BOD₁₀ = 76 % of Theoretical (2.44 g O₂/g test substance).
BOD₂₀ = 83 % of Theoretical (2.44 g O₂/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 Sewage Treatment

Comments: No Data Available.

5.1.3 Stability in Air (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES []
NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 Stability in Water (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES []
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 Identification of Main Mode of Degradability in Actual Use

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES ☐

NO ☒

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 **Ecotoxicological Data**

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static ☒, semi-static ☐, flow-through ☐
Other (e.g., field observation) ☐

GLP: YES ☐
NO ☒

Test Results: $LC_{50} = 70$ mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES ☐
NO ☐

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: *Daphnia magna* (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES ☐
NO ☒

Test Results: 48 hr EC₅₀ = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC₀ = 62.5 mg/L, 48 hr EC₁₀₀ = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC₀ - highest tested concentration without effect after 48 hours. EC₁₀₀ - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengesellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES ☐
NO ☐

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES []
NO [X]

Test Results:

72 hr EbC ₁₀	= 32.543 mg/L
72 hr EbC ₅₀	= 60.511 mg/L
96 hr EbC ₁₀	= 24.496 mg/L
96 hr EbC ₅₀	= 40.616 mg/L
72 hr EuC ₁₀	= 31.940 mg/L
72 hr EuC ₅₀	= 49.279 mg/L
96 hr EuC ₁₀	= 27.938 mg/L
96 hr EuC ₅₀	= 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES []
NO []

Test Results: No Data Available.

Comments:

Reference:

6.5 Toxicity to Bacteria

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES ☐
NO ☐

Test Results: No Data Available.

Comments:

Reference:

*** 6.6 Toxicity to Terrestrial Organisms**

6.6.1 Toxicity to Soil Dwelling Organisms

Test Results: No Data Available.

6.6.2 Toxicity to Plants

Test Results: No Data Available.

6.6.3 Toxicity to Birds

Test Results: No Data Available.

6.7 Biological Effects Monitoring (Including Biomagnification)

Test Results: No Data Available.

6.8 Biotransformation and Kinetics in Environmental Species

No Data Available.

7.0 Toxicological Data (oral, dermal and inhalation, as appropriate)

*** 7.1 Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES ☐
NO ☒

Test Results: Discriminating dose (for fixed dose only): LD₅₀ = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity (Additional Study)**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES ☐
NO ☒

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD₅₀ or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES ☒
NO ☐

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test):
1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES ☐
NO ☒

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report).
Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 Acute Dermal Toxicity

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES ☐
NO ☒

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, *J. Ind. Hyg. Toxicol.* 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES ☐
NO ☒

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance:** 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES []
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES ☒
NO ☐

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES ☐
NO ☒

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, *J. Ind. Hyg. Toxicol.* 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES ☐
NO ☐

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES []
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity (Additional Study)**

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES []
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. *Toxicol. Lett.* 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES ☒
NO ☐

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each

animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES ☒
NO ☐

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized *in extremis*. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES ☒
NO ☐

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid-, and high-dose groups, respectively. One male from the mid-dose group was found dead

during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES ☒
NO ☐

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid-, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and mid-dose groups. Absolute and relative (to body weight) liver weight were

significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES ☒
NO ☐

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid-, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte

hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity (Preferred Study)**

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES ☒
NO ☐

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid-, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights

occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: *S. typhimurium* TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES ☐
NO ☒

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: *Salmonella typhimurium*/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES ☐
NO ☒

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). *Salmonella* Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES ☐
NO ☐

Test Results: No Data Available.

Comments:

Reference:

7.5.3 Non-Bacterial Test *In Vivo*

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO []

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: The data from 2-ethylhexanol is directly applicable to the assessment of this endpoint for 2-ethylhexanoic acid due to the extensive metabolism of the former to the latter in vivo. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 Carcinogenicity

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES ☐
NO ☐

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES ☐
NO ☒

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size

in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES ☐
NO ☒

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethylhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. *Teratol.* 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES ☐
NO ☒

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryoletality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryoletality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. *Life Sci.* 46, 513-518.

(C.) Teratogenicity/Developmental Toxicity (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES ☐
NO ☒

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. *Fundam. Appl. Toxicol.* 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrIBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour period; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES ☐
NO ☒

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage

of resorptions increased at higher dose levels, and was also high in the animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or

clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. *Toxicol. Appl. Pharmacol.* 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES ☒
NO ☐

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae,

bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbancic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. *Fundam. Appl. Toxicol.* 20:199-209.

- (F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO []

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of

animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbancic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. *Fundam. Appl. Toxicol.* 20:199-209.

(G.) Teratogenicity/Developmental toxicity (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into

three groups and fed diets as described for the second experiment. The animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg) was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES []
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Comisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. *Teratology* 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxicokinetics

Test Substance: [2-¹⁴C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmol) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO []

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid

Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 Experience with Human Exposure (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 Biological Monitoring (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m³ (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the

work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3 ; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be $2.33 \times 10^{-4} \text{ mg/kilogram body weight/8 hour workday}$. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. *Int. Arch. Occup. Environ. Health*, 62:213-216.

9.0 **Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets**

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 **Availability and Reference(s) for Existing Review(s)**

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

1. General Information

ID 10026-11-6

Date August 11, 2005

1.0 SUBSTANCE INFORMATION

Generic Name : Zirconium tetrachloride
Chemical Name : Zirconium tetrachloride; zirconium (IV) chloride
CAS Registry No. : 10026-11-6
Component CAS Nos. :
EINECS No. :
Structural Formula : Cl_4Zr
Molecular Weight : 233.032
Synonyms and :
Tradenames :
References : <http://www.chemfinder.com>

201-161425

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2. Physico-Chemical Data

ID 10026-11-6

Date August 11, 2005

2.1 MELTING POINT

Type :
Guideline/method :
Value : 437°C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference : <http://www.chemfinder.com>

2.2 BOILING POINT

Type :
Guideline/method :
Value :
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : 2.803 at 15°C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability : (2) Reliable with restrictions. Source is well established data compendium.
Reference : Weast, R.C., (ed.), Handbook of Chemistry and Physics, 69th ed., 1988-1989.

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : 1 mm Hg at 190°C
Decomposition :
Year :

2. Physico-Chemical Data

ID 10026-11-6

Date August 11, 2005

GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability : (2) Reliable with restrictions. Source is well established data compendium.
Reference : Weast, R.C., (ed.), Handbook of Chemistry and Physics, 69th ed., 1988-1989.

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Partition coefficient not applicable; test substance dissociates in water
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : Soluble in cold water
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : Zirconium tetrachloride is extremely hygroscopic and forms zirconium oxychloride and hydrochloric acid in water (Budavari, S., ed. The Merck Index, 1989).
Reliability : (2) Reliable with restrictions. Source is well established data compendium.
Reference : Weast, R.C., (ed.), Handbook of Chemistry and Physics, 69th ed., 1988-1989.

2.7 FLASH POINT

Type :

2. Physico-Chemical Data

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Guideline/method	:
Value	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

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3.1.1 PHOTODEGRADATION

Type	:			
Guideline/method	:			
Light source	:			
Light spectrum	:			
Relative intensity	:		based on	
Spectrum of substance	:	lambda (max, >295nm)	:	
		epsilon (max)	:	
		epsilon (295)	:	
Conc. of substance	:		at	°C
DIRECT PHOTOLYSIS				
Half-life (t1/2)	:			
Degradation	:	% after		
Quantum yield	:			
INDIRECT PHOTOLYSIS				
Sensitizer	:			
Conc. of sensitizer	:			
Rate constant	:			
Degradation	:			
Deg. product	:			
Year	:			
GLP	:			
Test substance	:			
Deg. products CAS#	:			
Method	:			
Method detail	:			
Result	:			
Remark	:			
Reliability	:			
Reference	:			

3.1.2 DISSOCIATION

Type	:
Guideline/method	:
pKa	:
Year	:
GLP	:
Test substance	:
Approximate water solubility	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	

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Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method : Not applicable – metal does not degrade
Method detail :
Result :
Remark :
Reliability :
Reference :

3.7 BIOCONCENTRATION

3. Environmental Fate & Transport

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Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	In aquatic animals, bioaccumulation factors vary between 1 and 1600; however, values are generally less than 200.
Reliability	:	
Reference	:	Couture, P., C. Blaise, D. Cluis, and C. Bastien, 1989. Zirconium toxicity assessment using bacteria, algae, and fish assays. Water, Air, and Soil Pollution 47:87-100.

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4.1 ACUTE TOXICITY TO FISH

Type	: Acute toxicity to fish. Static exposure.
Guideline/method	:
Species	: <i>Oncorhynchus mykiss</i> (rainbow trout, freshwater)
Exposure period	: 96 hours
NOEC	:
LC0	:
LC50	: LC50 greater than 20 mg Zr/L.
LC100	:
Other	: Sublethal effects threshold > 20 mg/L
Other	:
Other	:
Limit test	:
Analytical monitoring	: None
Year	: 1989
GLP	: Not reported
Test substance	: Zirconium tetrachloride
Method	: Environment Canada, 1980. Standard procedure for testing the acute lethality of liquid effluents, Environment Protection Service, Report EPS 1 WP-80-1, Ottawa, Ontario, 11 p.
Method detail	: Young hatchery-purchased fry (6.2 ± 0.7 cm; 1.7 ± 0.7 g) were acclimated for at least 3 weeks to activated charcoal and ultraviolet light treated city water with a hardness of 100 – 150 mg CaCO ₃ . Fish (10 per concentration) were exposed to 0, 0.01, 0.1, 1, 10 and 100 mg Zr/L at 15°C with aeration of each test vessel. Mortality observations were made at 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72 and 96 hours. Dissolved oxygen, temperature, and pH were periodically monitored. A second assay examined the sublethal threshold concentration based upon the measurement of ATP as a biochemical indicator of energy stress in white muscle tissue. In this assay, 10 fish were exposed to 0, 1, 5 and 20 mg Zr/L. After exposure, the ATP content of white muscle tissue in 5 fish from each exposed group was examined and compared to controls.
Result	: Complete mortality occurred at the 100 mg/L concentration; however, this was attributable to the lethal pH of the test solution (3.0). Complete mortality also occurred in dilution water adjusted to a pH of 3.0. At the next lowest concentration, 10 mg/L (pH = 6.7) no lethal effects were observed. Coupled with the results of the sublethal assay, the 96-hr LC50 was reported as > 20 mg Zr/L. In the sublethal assay, no change in ATP levels in Zr-exposed fish, relative to controls, was observed. Therefore, the 96-hr minimal ATP stress concentration threshold for Zr is greater than 20 mg/L.
Remark	: An LC50 of greater than 10 mg Zr/L was reported for both 96- and 240-hr exposures of Coho salmon (<i>Oncorhynchus kisutch</i>) fingerlings (Peterson et al., 1976, as cited in Couture et al., 1989). For the zirconium salt of sulfuric acid, the 96-h LC50 for <i>Pimephales promelas</i> was reported to be 14 – 145 mg Zr/L; for zirconium oxychloride, the 96-h LC50 for <i>Lepomis macrochirus</i> was reported to be 15 – 270 mg Zr/L and for <i>Pimephales promelas</i> , 18 – 240 mg Zr/L. (ECOTOX database, 2005).
Reliability	: (2) Reliable with restrictions. Acute toxicity study conducted according to standardized procedures, methods and results adequately described in a peer-reviewed publication.
Reference	: Couture, P., C. Blaise, D. Cluis, and C. Bastien, 1989. Zirconium toxicity assessment using bacteria, algae, and fish assays. <i>Water, Air, and Soil Pollution</i> 47:87-100.

4. Ecotoxicity

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4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Acute toxicity to daphnids. Static exposure.
Guideline/method :
Species : *Daphnia magna*
Exposure period : 3 weeks
NOEC :
EC0 :
EC50 : LC50: 2 mg Zr/L
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring : None reported
Year : 1974
GLP : Not reported
Test substance : Zirconium chloride
Method :
Method detail :
Result : LC50 reported to be 2 mg Zr/L
Remark :
Reliability : (3) Not reliable. Non-standard endpoint, lack of detail on methods (secondary reference).
Reference : U.S. EPA, ECOTOX database, 2002.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type : Algal acute toxicity test
Guideline/method :
Species : *Selenastrum capricornutum* (freshwater green alga)
Endpoint : Population density
Exposure period : 96 hours
NOEC :
LOEC :
EC0 :
EC10 :
EC50 : 2.6 mg/L (mean of four tests). Values for each test: 2.1, 3.8, 2.9, and 1.7 mg Zr/L
Other : For 4 and 16 hour exposures in the ATP energy stress test, EC50s ranged from 1.3 to >2.5 mg Zr/L.
Other :
Other :
Limit test :
Analytical monitoring : None reported
Year : 1989
GLP : Not reported
Test substance : Zirconium tetrachloride.
Method : 96-well microtiter microplate method (Blaise et al., 1986, Tox. Assess. 1:261)
Method detail : Eleven serial dilutions (10, 5, 2.5, 1.25, 0.625, and so on) were tested with 8 replicates of each concentration and control. Four such tests were performed. In addition, confirmatory tests consisting of acute 4- and 16-hr ATP energy stress bioassays were conducted using the 96-well microplate technique, but with the inoculum increased to 10^6 cells/mL, with 4 replicates for each Zr concentration tested (10, 5, 2.5, 1.26, 0.625, 0.313, 0.156 mg/L) and nutrient spikes with and without Na₂EDTA and water. for each test

- concentration and controls. Aliquots of 0.1 mL were removed at 4 and 16 hours and relative light units (RLU) emitted from algal ATP cellular content measured luminometrically. RLUs and cell counts were then used as the basis for determining EC50s at 4 and 16 hours.
- Result** : The results of the four 96-hour population growth tests were similar, with a mean EC50 of 2.6 mg/L. The rapid ATP energy stress test was conducted to distinguish between growth inhibition due to unavailability of phosphorus due to inactivation by Zr, or actual toxicity attributable to Zr. The results confirmed the toxic effect of Zr.
- Remark** : In study with the green alga *Chlorella pyrenoidosa*, inorganic Zr compounds (including zirconium oxychloride) and organic Zr compounds resulted in a slight insignificant inhibitory effect upon growth rate; however, photosynthetic pigments were reduced by 13 – 33% in Zr-treated cultures. (Simon et al., Effects of zirconium on the growth and photosynthetic pigment composition of *Chlorella pyrenoidosa* green algae, Journal of Plant Nutrition 24(1):159-174.
- Reliability** : (2) Reliable with restrictions. Although the 96-well microplate technique is not as widely used as the bottle test method, it is an acceptable standard method. Experimental design and interpretation of results are adequately described in a peer-reviewed publication.
- Reference** : Couture, P., C. Blaise, D. Cluis, and C. Bastien, 1989. Zirconium toxicity assessment using bacteria, algae, and fish assays. Water, Air, and Soil Pollution 47:87-100.

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5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1 st . 2 nd . 3 rd .
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zirconium salts when parenterally administered are slowly absorbed from injection sites and simple cationic salts cause local irritation. Intravenously injected cationic salts form insoluble colloidal polymers and are phagocytized by macrophages. Young rats absorb more parenterally injected zirconium salts than adult or old animals, and young rats retain them longer in their skeleton because of vigorous metabolism in bone marrow. Excretion is mainly through feces, owing to poor alimentary absorption of orally-ingested zirconium salts and to the accumulation of soluble zirconium salts in the liver with their subsequent return to the alimentary tract by the bile. Less than 1% of the daily intake of zirconium of humans is excreted in urine. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly. A mechanism of zirconium homeostasis is apparently present in humans. (Hazardous Substances Data Bank, online at , subsequently referred to as HSDB, 2005). In studies with rats, a small fraction of orally administered zirconium was absorbed and selectively fixed in the ovaries, and to a lesser degree in the lung and bone. Excretion is mainly through the feces (for the non-absorbed zirconium) and through the urine (for the absorbed zirconium). (DeLongeas, J.-L., D. Burnel, P. Netter, M. Grignon, J.-M. Mur, R.-J. Royer, and G. Grignon, 1983. Toxicité et pharmacocinétique de l'oxychlorure de zirconium chez la souris et chez le rat, J. Pharmacol. 14(4):437-447). The biochemical properties of zirconium include a high affinity for phosphate groups and an inhibitory effect on many enzymes (Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100).

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Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type : Acute LD50
Guideline/Method :
Species : Mouse
Strain : Swiss
Sex : Female
Number of animals : 24
Vehicle : Distilled water for zirconium oxychloride and zirconium chloride; suspension of zirconium oxide.
Doses : Chosen in a geometric progression, but not specified. Doses analytically verified.
LD50 : 0.438 g/kg (95% confidence limits 0.412 – 0.489) for zirconium chloride; 1.227 g/kg (95% confidence limits 1.053 – 1.549) for zirconium oxychloride; >8.88 g/kg for zirconium oxide.
Year : 1983
GLP : Not reported
Test substance : Zirconium chloride, zirconium oxychloride and zirconium oxide.
Method :
Method detail : Animals (20 ± 1 g) were fasted prior to dosing and administered the test material, dissolved in distilled water for zirconium oxychloride and zirconium chloride or as a suspension of zirconium oxide. Observed for 14-days post-exposure.
Result : Some of the animals that died in the 24 hours following administration of the test substance exhibited convulsions. For those that survived beyond 24 hours but died before 14 days, the general behavior was marked by a lack of appetite, progressive weight loss, prostration and dull coat. Upon autopsy, observations included frequent digestive necroses and less frequent sometimes pulmonary necroses (particularly with zirconium chloride). All of the problems observed were more evident with zirconium chloride than zirconium oxychloride.
Remark : Zirconium salts are reported to have low oral toxicity; both the tetrachloride and oxychloride are poorly adsorbed and therefore have low oral toxicities with LD50 values in the rat of 0.7 g/kg and 3.5 g/kg, respectively. Toxicity is increased by intraperitoneal injection (LD50 of 400 mg/kg in rats for zirconium oxychloride. (Gosselin et al., as cited in HSDB, 2005). Oral LD50 values for zirconium for the mouse and rat have been reported as 0.655 g/kg and 1.688 g/kg, respectively (Budavari et al., as cited in HDSB, 2005).
Reliability : (2) Reliable with restrictions. Study details not fully described. Peer-reviewed publication.
Reference : DeLongeas, J.-L., D. Burnel, P. Netter, M. Grignon, J.-M. Mur, R.-J. Royer, and G. Grignon, 1983. Toxicité et pharmacocinétique de l'oxychlorure de zirconium chez la souris et chez le rat, J. Pharmacol. 14(4):437-447.

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :

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Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Inhalation of zirconium tetrachloride mist at an airborne concentration of 6 mg of Zr/m ³ for 60 days produced slight decreases in hemoglobin and red blood cell count in dogs, and increased mortality in rats and guinea pigs (Seiler et al., cited in HSDB, 2005)
Reliability	:	
Reference	:	

5.1.3 ACUTE DERMAL TOXICITY

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Number of animals	:
Vehicle	:
Doses	:
LD50	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Zirconium tetrachloride did not cause any sensitization responses in guinea pigs. Zirconium chloride caused mild lymph node responses in the sensitive

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mouse lymph node assay but was classified as a nonsensitizer (HSDB, 2005). Dermal exposure to zirconium in topical poison ivy medications and deodorants has caused granulomatous lesions, probably due to a hypersensitivity reaction. (HSDB, 2005).

Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Zirconium and its compounds are eye irritants (HSDB, 2005).
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species : Rat
Strain : Wistar
Sex : Female
Number of animals : 12 per group
Route of admin. : Gastric tube
Exposure period : 16 days
Frequency of treatment : Daily
Post exposure period : One month
Doses : 0.8 g zirconium oxychloride/kg b.w. (0.23 g zirconium/kg), confirmed analytically
Control group : yes
NOAEL :
LOAEL :
Other :
Year : 1983
GLP : Not reported
Test substance : Zirconium oxychloride
Method :
Method detail : 12 animals (weighing 150 g), individually housed, received 0.8 g zirconium oxychloride/kg body weight (0.23 g zirconium/kg) in 0.5 mL distilled water via gastric tube at the same time each day. Controls (12 rats) received the same volume of water only. Animals were allowed drinking water ad libitum one hour after gavage. Water consumption and urine production were

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	measured each day and animals weighed every other day. At the end of the exposure period (16 days), histopathology was conducted on tissues from 7 rats from each group (digestive tract fluid, kidney, liver, lung, ovaries, central nervous system). The 5 rats remaining for each group were observed for an additional month, then sacrificed for examination of the same tissues.
Result	: No mortalities or behavioral effects occurred during the experiment. No significant effect upon growth was observed. The histopathology revealed no differences between treated animals and controls with the exception of ovarian tissue, which was hypervascularized even one month after the end of the exposure period.
Remark	: In life-time studies in rats in which zirconium sulfate was administered at a level of 5 ppm in their drinking water and in which the solid diet contained an additional 2.6 ppm, state unknown, no evidence was found of any biological or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner (HSDB, 2005).
Reliability	: (2) Reliable with restrictions. Only one dose used, NOAEL not defined. Peer-reviewed publication.
Reference	: DeLongeas, J.-L., D. Burnel, P. Netter, M. Grignon, J.-M. Mur, R.-J. Royer, and G. Grignon, 1983. Toxicité et pharmacocinétique de l'oxychlorure de zirconium chez la souris et chez le rat, J. Pharmacol. 14(4):437-447.

5.5 GENETIC TOXICITY 'IN VITRO'

Type	: Mutagenicity
Guideline/method	:
System of testing	: His ⁺ reversion fluctuation assay
Species	: <i>Salmonella typhimurium</i>
Strain	: TA97, TA100, and TA102
Test concentrations	: 0, 0.01, 0.1, 1.0, and 10 mg Zr/L
Cytotoxic concentr.	:
Metabolic activation	: None
Year	: 1989
GLP	: Not reported
Test substance	: Zirconium tetrachloride
Method	: Followed method of Ames et. al.
Method detail	: Carried out in 96-well microtiter plates following the method of Green, M., Muriel, W. and Bridges, B., 1976, Mutation Res. 38:33. After 72-h incubation at 37°C, each microplate was scored for positive wells, as indicated by a color change from purple to yellow of the pH indicator bromocresol purple as a result of cellular growth by His ⁺ revertants.
Result	: Negative
Remark	: No significant differences in reversions relative to the controls; no dose-related effects on mutations seen.
Reliability	: (2) Reliable with restrictions. Basic data provided. Peer-reviewed publication.
Reference	: Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100.
Type	: Mutagenicity
Guideline/method	:
System of testing	: Bacterial DNA damage or repair assay (SOS Chromotest)
Species	: <i>Escherichia coli</i>
Strain	: Strain PQ37
Test concentrations	: 7 serial dilutions, 1.7 to 110 nM
Cytotoxic concentr.	:

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Metabolic activation	:	With and without S9
Year	:	1989
GLP	:	Not reported
Test substance	:	Zirconium tetrachloride
Method	:	Followed method of Quillardet, P. and Hofnung, M., 1985, Mutation Res. 147:65
Method detail	:	Measured β -galactosidase production by colorimetry after 2.5 hr exposure using a 96-well microtiter plate kit (Orgenics, Ltd., Yavne, Israel).
Result	:	No observable increase in the induction factor noted at any of the concentrations tested.
Remark	:	
Reliability	:	(2) Reliable with restrictions. Basic data provided. Peer-reviewed publication.
Reference	:	Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100.
Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Ames assay, standard plate assay
Species	:	<i>Salmonella typhimurium</i>
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	100 – 10,000 μ g/plate (with activation); 33-3333 μ g/plate (without activation). Dissolved in DMSO.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. Metabolic activation using Aroclor 1254-induced S-9 liver fractions of both rats and hamsters.
Year	:	
GLP	:	
Test substance	:	Zirconium oxychloride
Method	:	Followed method of Ames et. al.
Method detail	:	
Result	:	Negative
Remark	:	Zirconium oxychloride hexahydrate was also negative when tested in the Ames assay, both with and without activation (CCRIS database, HSDB, 2005).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	CCRIS database (HSDB, 2005).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	
Guideline/method	:	
Species	:	Mouse
Strain	:	Swiss albino
Sex	:	Male and female
Number of animals	:	
Route of admin.	:	Oral
Exposure period	:	6 – 24 hours
Doses	:	220 -225, 734 – 750, and 2220 – 2250 mg/kg.
Year	:	1991
GLP	:	Not reported
Test substance	:	Zirconium oxychloride in aqueous solution
Method	:	
Method detail	:	Mice of both sexes, 8-9 weeks old and weighing 25 – 30 g were used, with 5 of each sex per group. A single oral administration of zirconium oxychloride was given at dose levels of 1/20, 1/6 and 1/2 of the LD50. These

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	dose levels were 220 -225 mg/kg, 734 - 750 mg/kg, and 2220 – 2250 mg/kg. Control animals received distilled water. Animals were sacrificed and bone marrow fixed and stained for analysis of chromosomal abnormalities at 6, 12, and 24 hours after dosing. Slides were coded and scored blind, with 50 well-scattered metaphase plates per animal and a total of 250 metaphase plates per sex per treatment group scored. Types of aberrations were scored and recorded according to Tice et al., 1987. Environ. Mutag. 9:37-58.
Result	: Significant increases in chromosomal aberrations and breaks per cell were observed in male mice 12 and 24 hours after administration of zirconium oxychloride and in female mice 6, 12, and 24 hours after administration. In both sexes, the increase was directly proportional to the concentrations used. Female mice were more susceptible than males, although not significantly so.
Remark	: Zirconium oxychloride caused dose-dependent enhancement of the occurrence of chromosomal aberrations and sister chromatid exchanges in human peripheral blood leucocytes (Ghosh, S., and Talukder, G., and Sharma, A. 1991. Cytogenetic effects of exposure to zirconium oxychloride in human leucocyte cultures, 1991. Toxicol. In Vitro 5(4):295-299.
Reliability	: (2) Reliable with restrictions. Sound scientific approach.
Reference	: Ghosh, S. Sharma, A. and Talukder, G., 1991. Relationship of clastogenic effects of zirconium oxychloride to dose and duration of exposure in bone marrow cells of mice in vivo. Toxicology Letters 55:195-201.

5.8.2 DEVELOPMENTAL TOXICITY

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
NOAEL maternal tox.	:
NOAEL teratogen.	:
Other	:
Other	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

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5.8.3 TOXICITY TO REPRODUCTION

Type	:
Guideline/method	:
In vitro/in vivo	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

6.0 OTHER INFORMATION

An enhanced response of immunoglobulin-M (IgM) antibody production was observed in mice intraperitoneally injected with zirconium oxychloride at low doses (1/40 to 1/80 of the LD50). The study authors concluded that these findings suggest that long term exposure to zirconium may enhance the humoral immune response and induce a state of hypersensitivity (Shima, S., Morita, K., Tachikawa, S., Ito, T., Kurita, H., Yoshida, T., Kato, Y., and Yamamoto, Y., 1987. IgM antibody production in mice intraperitoneally injected with zirconium oxychloride. British Journal of Industrial Medicine 44(9):633-637.

6.1 CARCINOGENICITY

Zirconium sulfate was administered at a level of 5 ppm in drinking water in lifetime studies in rats. The diet contained an additional 2.66 ppm of an unknown Zr moiety. No evidence was found of any biological or toxicological activity of zirconium, except to affect inconsistently the body weight of older animals. There was also no evidence that zirconium was tumorigenic in a rat strain (Long-Evans) with appreciable (20%) tumor incidence (HSDB, 2005).

1. General Information

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201-161420

1.0 SUBSTANCE INFORMATION

Generic Name : Hexanoic acid, 2-ethyl, zirconium salt
Chemical Name : Hexanoic acid, 2-ethyl, zirconium salt
CAS Registry No. : 22464-99-9
Component CAS Nos. :
EINECS No. :
Structural Formula : $C_{18}H_{30}O_5Zr$
Molecular Weight : 393.63
Synonyms and Tradenames : Zirconium 2-ethylhexanoate; Zirconium octoate; Zirconyl 2-ethylhexanoate
References : <http://www.chemfinder.com>; MSDS prepared by The Shepherd Chemical Company, dated 5/15/01.

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2. Physico-Chemical Data

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2.1 MELTING POINT

Type	: Melting Point/Melting Range Determination
Guideline/method	: OECD 102; EEC Directive 92/69, and EPA Guideline OPPTS 830.7200
Value	: Freezing point < -75°C, the test material does not freeze under the conditions of the test.
Decomposition	: NA
Sublimation	: NA
Year	: 2003
GLP	: Yes
Test substance	: Hexanoic acid, 2-ethyl, zirconium salt, batch B10N43, 96+% purity, viscous amber colored liquid
Method	: OECD 102 Melting Point/Melting Range, July 1995, capillary method
Method detail	: 4ml of test material was placed in a test tube and cooled down to -75°C using dry ice and 2-propanol. Measurements of temperature were taken at regular intervals as the sample was cooled and the physical state of the sample was monitored visually.
Result	: At room temperature the test item was yellow to brown and clear. At -75°C the test item was turbid and viscous and was still moveable. The test was run in duplicate. It was not possible to determine the precise freezing point under the conditions of this test. The freezing point is < -75°C.
Remark	: Supporting data for dissociation products: Acid: Melting point is reported as -118.4°C for 2-ethylhexanoic acid (Appendix B) Metal: Melting point is reported as 437°C for zirconium tetrachloride (Appendix C).
Reliability	: (1) Reliable without restriction
Reference	: Tognucci, A., 2003

2.2 BOILING POINT

Type	: Boiling point/boiling range determination
Guideline/method	: OECD 103; EPA OPPTS 830.7220
Value	: 204.5 – 206.8°C
Decomposition	:
Year	: 2003
GLP	: Yes
Test substance	: Hexanoic acid, 2-ethyl, zirconium salt, batch B10N43, 96+% purity, viscous amber colored liquid
Method	: OECD 102, Boiling Point, 1995 (thermal analysis using calorimeter); EPA Product Properties Test Guidelines OPPTS 830.7220, Boiling point/Boiling rate, August 1996.
Method detail	: In the preliminary test, 7.10 mg of test material was placed in an aluminum cup and heated from 25°C to 400°C at a rate of 20 K/min. The quantities of heat absorbed or released were measured and recorded using a Differential Scanning Colorimeter, DSC 821, Mettler Toledo. In the main study, the thermal analysis was repeated in the immediate vicinity of the peak temperature observed in the preliminary test. For the actual determination of boiling point, the temperature rise was adjusted to 5 K/min. over the range 150 - 280°C (first run) and 10 K/min. over the range 180 - 250°C (second run). All tests were performed in an air atmosphere, with the weight and appearance of the sample were recorded before and after heating. Atmospheric pressure during the main test was 98.5 kPa.
Result	: During the preliminary test, an endothermic heat effect (boiling) was observed between 207°C and 220°C with an exothermic heat effect starting at about 345°C. Afterwards, the sample lost 67% of mass and the cup was

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empty, with a black and foamed residue on the cover. In the main test, the samples lost 54% (first run) and 42% (second run) of their mass, and the sample was viscous and brown-colored afterwards. The boiling point was determined to be between 204.5°C and 206.8°C.

Remark : **Supporting data for dissociation products:**
Acid: Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (Appendix B)

Reliability : (1) Reliable without restriction

Reference : Tognucci, A., 2003. Determination of the boiling point/boiling range of Hexanoic acid, 2-ethyl, zirconium salt, RCC Study No. 849081, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

2.3 DENSITY

Type :
Guideline/method :
Value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: The reported density for zirconium tetrachloride is 2.803 at 15°C (Appendix C).

Reliability :
Reference :

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value :
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Vapor pressure is reported as 1.33×10^{-3} kPa at 20°C for 2-ethylhexanoic acid (Appendix B).
Metal: The reported vapor pressure for zirconium tetrachloride is 1 mm Hg at 190°C (Appendix C).

Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method : WSKOW v1.41 (EPIWIN v3.11)
Partition coefficient :
Log Pow : 4.37
pH value :
Year :

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GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (Appendix B).
Reliability : (1) Reliable without restriction; Calculated using scientifically acceptable method
Reference :

2.6.1 SOLUBILITY IN WATER

Type : Water Solubility Determination
Guideline/method : OECD 105; EPA OPPTS 830.7840
Value : 0.5 µg/L at 20°C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year : 2003
GLP : Yes
Test substance : Hexanoic acid, 2-ethyl, zirconium salt, batch B10N43, 96+% purity, viscous amber colored liquid
Deg. products CAS# :
Method : OECD 105, Water Solubility, 1995; EPA Product Properties Test Guidelines, OPPTS 830.7840, Water Solubility: Column Eution Method, Shake Flask Method, 1998.
Method detail : The flask shaking method was used. About 10 g of test item was weighed into each of 6 Erlenmeyer flasks and 500 mL water added. Flasks were capped and shaken at about 30°C for 24, 28 and 72 hours, followed by equilibration for 24 hours at 20 ± 0.5°C. The supernatant solutions were centrifuged (3700 g for 60 minutes) and filtered (0.2 µm). Samples were diluted with nitric acid and the amount of zirconium quantified using ICP-MS. Each sample was measured in triplicate.
Result : Based upon the results of six samples, the zirconium solubility was 0.09 ng/mL (SD = ± 0.03 ng/mL), which corresponds to a water solubility for Hexanoic acid, 2-ethyl, zirconium salt of 0.5 ng/mL (0.5 µg/L), calculated based upon zirconium content of 18.17% zirconium (w/w). Although the measured results differed by about 30%, considering the very low concentrations measured, this was considered to be acceptable.
Remark : **Supporting data for dissociation products:**
Acid: The water solubility of 2-ethylhexanoic acid was reported to be 25 mg/L at 25°C (Appendix B)
Metal: Zirconium tetrachloride is soluble in cold water; it is extremely hygroscopic and forms zirconium oxychloride and hydrochloric acid in water (Appendix C).
Reliability : (1) Reliable without restriction
Reference : Tognucci, A., 2003. Determination of the water solubility of Hexanoic acid, 2-ethyl, zirconium salt. RCC Study No. 849083, conducted for the Metal Carboxylates Coalition by RCC Ltd., Switzerland.

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2.7 FLASH POINT

Type :
Guideline/method :
Value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Reliability :
Reference :

Supporting data for dissociation products:

Acid: A flashpoint of 118°C was reported for 2-ethylhexanoic acid (Appendix B).

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3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Half-life (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : 2-ethylhexanoic acid is predicted to undergo indirect photolysis with a half-life of 16 hours, according to AOP v.1.91 in the EPIWIN v.311 program.
Reliability :
Reference :

3.1.2 DISSOCIATION

Type : Dissociation constant determination
Guideline/method : OECD 112
pKa : 5.81, 7.09, 7.65, and 8.24 at 20°C
Year : 2002
GLP : Yes
Test substance : Zirconium (IV) 2-ethylhexanoate, lot number 119L09, received from Alfa Aesar Chemical Company. Liquid, purity of 18.17% ZrO₂.
Approximate water solubility : 50 mg/L as determined visually in preliminary study
Method : OECD Guideline 112, Dissociation Constants in Water
Method detail : Three replicate samples of zirconium(IV) 2-ethylhexanoate were prepared at a nominal concentration of 25 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the first equivalence point and thereafter, a minimum of three incremental additions were made before each of the three remaining equivalence points. The titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 3 points for each equivalence point on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

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Result : Mean (N = 3) pKa values were 5.81 (SD = 0.0806), 7.09 (SD = 0.0491), 7.65 (SD = 0.0689), and 8.24 (SD = 0.0299) at 20°C

Remark : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : (1) Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of zirconium (IV) 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-104, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid:
Assuming equal distribution to all compartments, the Level III Fugacity Model (EPIWIN v3.11) predicts distribution of 2-ethylhexanoic acid as follows: 5.29% to air, 41.6% to water, 53% to soil, and 0.197% to sediment. The predicted persistence time is 190 hours.

Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :

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Kinetic of test subst. : % (specify time and % degradation)

:
%
%
%
%

Control substance :

Kinetic :

%
%

Deg. product :

Year :

GLP :

Test substance :

Deg. products CAS# :

Method :

Method detail :

Result :

Remark :

Supporting data for dissociation products:

Acid: Aerobic biodegradation of 2-ethylhexanoic acid was reported from a study with non-acclimated activated sludge, similar to OECD Guideline 301D. The resulting BOD₅, BOD₁₀ and BOD₂₀, respectively, was 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (Appendix B).

Metal: metal does not degrade.

Reliability :

Reference :

3.7 BIOCONCENTRATION

Type :

Guideline/method :

Species :

Exposure period :

at °C

Concentration :

BCF :

Elimination :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark :

Supporting data for dissociation products:

Metal: In aquatic animals, bioaccumulation factors for zirconium vary between 1 and 1600; however, values are generally less than 200. (Appendix C).

Reliability :

Reference :

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4.1 ACUTE TOXICITY TO FISH

Type	: Acute toxicity to fish. Static exposure.
Guideline/method	:
Species	: <i>Lepomis macrochirus</i> (bluegill sunfish, freshwater)
Exposure period	: 96 hours
NOEC	:
LC0	:
LC50	: LC50 greater than tested concentration (100% of a 24% zirconium octoate solution).
LC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: None reported
Year	: 1981
GLP	: Not reported
Test substance	: Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	: United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	: Test concentrations were control and 100% concentration of a 24% zirconium octoate solution. Test conducted in reconstituted freshwater (hardness = soft water) and temperature range of 19 – 22.5°C. Fish were < 1 year old and of same age class. Biological loading was 0.3 g/L.
Result	: No mortality observed in 100% concentration of a 24% calcium octoate solution.
Remark	: Supporting data for dissociation products: Acid: The 96-h LC50 for fathead minnows (<i>Pimephales promelas</i>) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix B). Metal: For zirconium tetrachloride, the 96-h LC50 for rainbow trout (<i>Oncorhynchus mykiss</i>) was reported to be greater than 20 mg Zr/L and the sublethal effects threshold was greater than 20 mg Zr/L. An LC50 of greater than 10 mg/L was reported for both 96- and 240-hr exposures of Coho salmon (<i>Oncorhynchus kisutch</i>) fingerlings. For the zirconium salt of sulfuric acid, the 96-h LC50 for <i>Pimephales promelas</i> was reported to be 14 – 145 mg Zr/L; for zirconium oxychloride, the 96-h LC50 for <i>Lepomis macrochirus</i> was reported to be 15 – 270 mg Zr/L and for <i>Pimephales promelas</i> , 18 –240 mg Zr/L. (Appendix C)
Reliability	: (3) Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.
Type	: Acute toxicity to fish. Static exposure.
Guideline/method	:
Species	: <i>Cyprinodon variegatus</i> (sheepshead minnow, saltwater)
Exposure period	: 96 hours
NOEC	:

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LC0 :
LC50 : LC50 greater than tested concentration (100% of a 24% zirconium octoate solution).
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring : None reported
Year : 1981
GLP : Not reported
Test substance : Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method : United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail : Test concentrations were control and 100% concentration of a 24% zirconium octoate solution. Test conducted using synthetic seawater (28 ppt), temperature range of 20 - 22°C, fish < 1 yr old and of same age class, biological loading 0.9 g/L.
Result : No mortality observed in 100% concentration of a 24% calcium octoate solution.
Remark :
Reliability : (3) Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Acute toxicity to daphnids. Static exposure.
Guideline/method :
Species : *Daphnia magna*
Exposure period : 48 hours
NOEC :
EC0 :
EC50 : 48-h EC50: 58.1% (95% CI: 46 - 73.3%)
EC100 :
Other : 24-h EC50 could not be estimated because of insufficient mortality
Other :
Other :
Limit test :
Analytical monitoring : None reported
Year : 1981
GLP : Not reported
Test substance : Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method : United States Testing Company protocol PRO/FT, Daphnia, 365-0
Method detail : Test conducted in filtered (0.22 µ) lake water (hardness = soft), temperature range 19 - 21°C. Test concentrations were 0, 10, 18, 32, 56 and 100% of zirconium octoate (24% solution). No information on test organisms.

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Result	: 48-h EC50: 58.1% (95% CI: 46 – 73.3%); 24-h EC50: could not be calculated because of low mortality
Remark	: Supporting data for dissociation products: Acid: The 48-h EC50 for <i>Daphnia magna</i> for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix B). Metal: For zirconium chloride, the 3-week LC50 for <i>Daphnia magna</i> was reported to be 2 mg Zr/L (Appendix C).
Reliability	: (3) Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	: Algal acute toxicity test
Guideline/method	:
Species	: <i>Selenastrum capricornutum</i> (freshwater green alga)
Endpoint	: "growth" (not specified further; could be growth rate, yield, or viability)
Exposure period	: 96 hours
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	: 0.07%
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: None reported
Year	: 1981
GLP	: Not reported
Test substance	: Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	: United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail	: Test concentrations were 0, 0.6, 0.10, 0.18, 0.32 and 0.56%. Stock solution prepared by adding an excessive amount of zirconium octoate (24%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used freshwater algal maintenance medium and test temperature 19 - 20°C.
Result	: 96-h EC50 was 0.07%
Remark	: Supporting data for dissociation products: Acid: For the green alga <i>Scenedesmus subspicatus</i> , the 96-h E ₅₀ C50 (EC50 based upon biomass) was reported to be 40.616 mg/L and the 96-hE ₅₀ C50 (EC50 based upon growth rate) was reported to be 44.390 mg/L for 2-ethylhexanoic acid (Appendix B). Metal: For zirconium tetrachloride, the 96-h EC50 for <i>Selenastrum capricornutum</i> was reported to be 2.6 mg Zr/L (Appendix C).
Reliability	: (3) Not reliable. Test material inadequately described and reported to be

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	not soluble in water. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.
Type	: Algal acute toxicity test
Guideline/method	:
Species	: <i>Skeletonema costatum</i> (saltwater diatom)
Endpoint	: "growth" (not specified further; could be growth rate, yield, or viability)
Exposure period	: 96 hours
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	: 0.08%
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	: None reported
Year	: 1981
GLP	: Not reported
Test substance	: Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West -1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	: United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail	: Test concentrations were 0, 0.6, 0.10, 0.18, 0.32 and 0.56%. Stock solution prepared by adding an excessive amount of zirconium octoate (24%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used seawater algal medium I and test temperature 19 - 20°C
Result	: 96-h EC50 was 0.08%
Remark	:
Reliability	: (3) Not reliable. Test material inadequately described and reported to be not soluble in water. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.
Reference	: Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.4 ACUTE TOXICITY TO AVIAN SPECIES

Type	: Limit test
Guideline/method	:
Species	: Bobwhite quail (<i>Colinus virginianus</i>)

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Number, sex and age of animals	:	22 birds (11 males and 11 females), approximately 16 weeks old (200 ± 30 g)
Exposure period	:	14 days
NOEL	:	
LD50	:	> 2000 mg/kg
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	No
Test substance	:	Zirconium octoate, administered as a 20% w/v suspension in corn oil
Method	:	
Method detail	:	Birds were housed in metal cages with wire floors, under a photoperiod of 17 hours light and 7 hours dark, mean humidity of 71% and mean temperature of 20°C (range 14 - 28°C). Birds were provided with water and standard diet ad libitum (except overnight starvation prior to dosing). Dose levels included vehicle control and 2000 mg/kg, administered by oral gavage. Mortalities were recorded daily. Body weights were recorded prior to dosing and at days 3, 7 and 14. Food consumption was recorded weekly. All birds were examined at death or test termination for gross pathology.
Result	:	Following dosing, birds dosed with zirconium octoate were quiet and subdued, but recovered after 19 hours and remained in good health for the rest of the study. Body weight changes were considered to be within normal limits. Food consumption was similar in the dosed birds and the controls. No abnormalities were detected in any birds.
Remark	:	
Reliability	:	(3) Not reliable. Test material inadequately described. Secondary reference.
Reference	:	Previously abstracted information from studies conducted by Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Original study report not available.

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5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

Type :

Species :

Number of animals :

Males :

Females :

•

•

Males :

Females :

•

•

Route of administration :

Exposure time :

Product type guidance :

Decision on results on :

acute tox. tests

Adverse effects on :

prolonged exposure

Half-lives :

1st.

2nd:

3rd.

Toxic behavior :

Deg. product :

Deg. products CAS# :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark :

Acid: Radiolabeled 2-ethylhexanoic acid was administered to female rats as follows: a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs.

After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

<u>Route</u>	<u>Dose</u>	<u>Percentage Excreted as</u>
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid; 2% unmetabolized 2-Ethylhexanoic acid
Oral (single)	100 mg/kg	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid; 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid; 2% unmetabolized 2-Ethylhexanoic acid

(Appendix B).

Metal: Zirconium salts when parenterally administered are slowly absorbed from injection sites and simple cationic salts cause local irritation. Intravenously injected cationic salts form insoluble colloidal polymers and are phagocytized by macrophages. Young rats absorb more parenterally injected zirconium salts than adult or old animals, and young rats retain them longer in their skeleton because of vigorous metabolism in bone marrow. Excretion is mainly through feces, owing to poor alimentary absorption of orally-ingested zirconium salts and to the accumulation of soluble zirconium salts in the liver with their subsequent return to the alimentary tract by the bile. Less than 1% of the daily intake of zirconium of humans is excreted in urine. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly. A mechanism of zirconium

homeostasis is apparently present in humans. (Hazardous Substances Data Bank, online at , subsequently referred to as HSDB, 2002). In studies with rats, a small fraction of orally administered zirconium was absorbed and selectively fixed in the ovaries, and to a lesser degree in the lung and bone. Excretion is mainly through the feces (for the non-absorbed zirconium) and through the urine (for the absorbed zirconium). (DeLongeas, J.-L., D. Burnel, P. Netter, M. Grignon, J.-M. Mur, R.-J. Royer, and G. Grignon, 1983. Toxicité et pharmacocinétique de l'oxychlorure de zirconium chez la souris et chez le rat, J. Pharmacol. 14(4):437-447). The biochemical properties of zirconium include a high affinity for phosphate groups and an inhibitory effect on many enzymes (Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100)..

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type : Limit Test
Guideline/Method :
Species : Rat
Strain : Sherman-Wistar albino
Sex : Male and female
Number of animals : 10 (5 male, 5 female)
Vehicle :
Doses : 5.0 g/kg
LD50 : >5.0 g/kg for both males and females.
Year : 1980
GLP : Not reported
Test substance : Zirconium octoate, 24%, Lot # 28702. Density approx. 1.3 g/mL.
Method : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail : Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.
Result : No mortality observed. LD50 for both sexes > 5.0 g/kg For both sexes, within 1 hr following dosing, animals were slightly ataxic, depressed, ruffled, and drooling. After 2-3 hours they were semi-comatose to comatose. They remained severely depressed, ruffled, drooling and dirty for 2-3 days before beginning to recover. After 5 days the animals appeared essentially normal. Gross necropsies were unremarkable.
Remark : **Supporting data for dissociation products:**
Acid: The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (Appendix B).
Metal: Both the tetrachloride and oxychloride salts of zirconium are poorly adsorbed and therefore have low oral toxicities. The reported LD50 for the mouse is 0.438 g/kg for zirconium chloride and 1.227 g/kg for zirconium oxychloride. with LD50 values in the rat of 0.7 g/kg and 3.5 g/kg, respectively. (Appendix C).
Reliability : (2) Reliable with restrictions. Basic data provided, exposure conditions not fully described, test material not described. Comparable to guideline.
Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type : Limit Test

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Guideline/method	:	
Species	:	Rat
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	10 (5 male and 5 female)
Vehicle	:	
Doses	:	One concentration, 8.8 mg/L of a 50% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.
Exposure time	:	1 hour
LC50	:	> 8.8 mg/L (maximum attainable nominal concentration)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate 24% (Lot # 28702), prepared and used as a 50% w/v suspension in mineral spirits.
Method	:	
Method detail	:	Animals (200 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 70°F. Test material concentration was measured and determined to be 8.8 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 0.68 microns MMD (mass median diameter). Animals observed for 14 days post-exposure
Result	:	No adverse effects were observed during the exposure period or during the two-week post exposure period. No mortality, no toxicity, and no adverse gross necropsy findings
Remark	:	Supporting data for dissociation products: Acid: The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (Appendix BA). Metal: Inhalation of zirconium tetrachloride mist at an airborne concentration of 6 mg of Zr/m ³ for 60 days produced slight decreases in hemoglobin and red blood cell count in dogs, and increased mortality in rats and guinea pigs (Appendix C).
Reliability	:	(2) Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type	:	Limit Test
Guideline/method	:	
Species	:	Rabbit
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	Six (3 male and 3 female)
Vehicle	:	
Doses	:	One dose, 5 g/kg
LD50	:	> 5 g/kg
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702. Density approx. 1.3 g/mL.
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR

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Method detail	: Section 1500.40. Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure. Gross autopsies conducted on all dead and surviving animals.
Result	: No mortality or toxicity. No adverse gross necropsy findings in this limit test.
Remark	: Supporting data for dissocation products: Acid: The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg. (Appendix B). Metal: No data
Reliability	: (2) Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference	: Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type	: Primary skin irritation
Guideline/method	:
Species	: Rabbit, albino
Strain	:
Sex	:
Concentration	:
Exposure	:
Exposure time	:
Number of animals	: Six
Vehicle	:
Classification	: Not classified as a primary skin irritant
Year	: 1980
GLP	: Not reported
Test substance	: Zirconium octoate, 24%, Lot # 28702
Method	: Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.41.
Method detail	: Rabbits were clipped over a wide area. One side of the animals' backs was abraded at one site with a lancet sufficiently deep to penetrate the stratum corneum but not enter the derma to produce bleeding. A 0.5 mL portion of the test material was applied to an abraded and an intact skin site on the same animal. The treated areas were covered with gauze patches and an impervious material was wrapped around the trunks to hold the patches in place. After 24 hours, the wrapping was removed and the treated areas examined. Readings were also made after 72 hours. The Draize method of scoring was used.
Result	: The test substance was not a primary skin irritant to rabbits within the definition of the Federal Hazardous Substances Act. The primary irritation score was 0.96.
Remark	: Supporting data for dissocation products: Acid: 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (Appendix B).

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	Metal: Dermal exposure to zirconium in topical poison ivy medications and deodorants has caused granulomatous lesions, probably due to a hypersensitivity reaction. (Appendix C).
Reliability	: (2) Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	: Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.
Type	: Contact dermal irritation/sensitization
Guideline/method	:
Species	: Guinea pig
Strain	:
Sex	: Male, weighing 300 – 400 g
Concentration	:
Exposure	:
Exposure time	:
Number of animals	: 10
Vehicle	:
Classification	:
Year	: 1980
GLP	: Not reported
Test substance	: Zirconium octoate, 24%, Lot # 28702. The test substance was composed of 68.0% zirconium 2-ethylhexanoate, 24.2% mineral spirits and 7.8% other ingredients. It was a light yellow liquid with a mineral spirits odor.
Method	:
Method detail	: A 0.5 mL portion of material was applied to the intact skin test sites on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After 24 hours, the patch was removed, the animals allowed to rest for 1 day, and another application was made to the same skin site. This sequence was repeated for a total of 10 applications, after which time the animals were given a two week rest period. Subsequently a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for irritation using the Draize method of scoring, 24 hours after each induction application and 24 and 48 hours after the challenge application.
Result	: The test substance was a primary skin irritant and a fatiguing agent, but not a sensitizing agent.
Remark	: Supporting data for dissociation products: Acid: 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (Appendix B). Metal: Zirconium tetrachloride did not cause any sensitization responses in guinea pigs. Zirconium chloride caused mild lymph node responses in the sensitive mouse lymph node assay but was classified as a nonsensitizer. (Appendix C).
Reliability	: (2) Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	: Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 EYE IRRITATION

Type	: Primary eye irritation
Guideline/method	:
Species	: Rabbits, young adults
Strain	: Albino
Sex	:

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Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	Six
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702.
Method	:	
Method detail	:	0.1 mL of the test material was instilled into the right eyes of the animals while the other eye served as the untreated control. The test material was not washed from the eyes. The treated eyes were examined at 1, 2, 3, 5, and 7 days following exposure. Results were scored according to the Draize Scale of Scoring Ocular Lesions.
Result	:	The test substance was not a primary ocular irritant within the definition of the Federal Hazardous Substances Act.
Remark	:	Supporting data for dissociation products: Acid: 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours. No observations were made beyond 24 hours to assess recovery. (Appendix B). Metal: Zirconium and its compounds are eye irritants (Appendix C).
Reliability	:	(2) Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Supporting data for dissociation products: Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery. Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body

weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Study H, Appendix B). These data are consistent with four previous repeated dose studies in Fischer rats (Appendix B). In a similar 13-week dietary exposure study with B6C3F1 mice, the NOAEL was approximately 200 mg/kg-day (Study G, Appendix B).

Metal: Zirconium oxychloride (0.8 g/kg, equivalent to 0.23 g Zr/kg) did not affect survival, behavior or growth of rats dosed via gastric tube for 16 days. Histopathology was unremarkable with the exception of hypervascularization of ovarian tissue. In life-time studies in rats in which zirconium sulfate was administered at a level of 5 ppm in their drinking water and in which the solid diet contained an additional 2.6 ppm, state unknown, no evidence was found of any biologic or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner. (Appendix C).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Mutagenicity
Guideline/method :
System of testing : Ames assay, standard plate assay
Species : *Salmonella typhimurium*
Strain : TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations : 5, 10, 50, 100, and 500 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr. :
Metabolic activation : Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254, as per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year : 1981
GLP : No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance : Zirconium octoate, Lot No. 28702

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Method	: Followed method of Ames et. al.
Method detail	: 0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37°C and number of colonies compared to background. No further details provided.
Result	: Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of <i>S. typhimurium</i> tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response.
Remark	: Supporting data for dissociation products: Acid: In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid either with or without activation (Appendix B). Metal: No genotoxic effects of zirconium tetrachloride were seen using three <i>Salmonella</i> sp. strains in the His ⁺ reverse fluctuation assay, without activation. Zirconium oxychloride and zirconium oxychloride hexahydrate have been shown to have no mutagenic activity in the Ames assay, with various strains of <i>S. typhimurium</i> , both with and without activation. (Appendix C).
Reliability	: (2) Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	: Van Goethem, D., 1981. Evaluation of zirconium octoate in the <i>Salmonella</i> /Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).
Type	: Mutagenicity
Guideline/method	:
System of testing	: Bacterial DNA damage or repair assay
Species	: <i>Escherichia coli</i>
Strain	: W3110 (pol A ⁺) and its DNA polymerase deficient derivative p3478 (pol A)
Test concentrations	: 5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in DMSO.
Cytotoxic concentr.	:
Metabolic activation	: With and without. Activation with S-9 from Aroclor 1254 induced rat liver as per Ames al., 1975, Mut. Res. 31:347-364
Year	: 1981
GLP	: No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	: Zirconium octoate 24%, Lot No. 28702. Clear liquid, insoluble in water and various solvents. Because of insolubility, the actual material tested was a suspension of zirconium octoate, 24%, in dimethylsulfoxide (DMSO) and the DMSO soluble fraction, if any. Zirconium octoate 24% was suspended with vigorous vortexing in DMSO at 5 mg/mL.
Method	: Followed method of Rosenkranz et al. (1971).
Method detail	: Test material (5 concentrations) applied to cells in culture. Vehicle controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 µg/mL without activation and 2-aminofluorene at 200 µg/mL with activation). Bacteria (10 ⁴) of each strain were exposed to the test material for 1 hour at 37°C. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37°C and the number of viable cells determined.
Result	: Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A ⁺ to pol A ⁺ survivors), with or without activation. Survival index at all dose levels was greater than 0.80.
Remark	: Supporting data for dissociation products: Metal: Zirconium tetrachloride did not cause an observable increase in the induction of β-galactosidase in the SOS Chromotest using <i>E. coli</i> strain

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Reliability : PQ37, both with and without induction. (Appendix C).
Reference : (2) Reliable with restrictions. Basic data provided. Comparable to guideline.
: Van Goethem, D., 1981. Evaluation of zirconium octoate, 24%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus mutagenicity assay
Guideline/method :
Species : Mouse
Strain : Specific Pathogen Free mice of the COBS CD-1 (ICR) BR (ICR derived) strain
Sex : Male and female
Number of animals : 5 males and 5 females per dose level (including vehicle control and positive control)
Route of admin. : Oral gavage, using corn oil vehicle
Exposure period : Thirty hours (dosing at 0 and 24 hours, followed by 6 hours observation)
Doses : 1250, 2500 and 5000 mg/kg, given twice (24 hours apart) to produce total dose levels of 2500, 5000 and 10000 mg/kg. Corn oil control (0.1 mL/10g via gavage) and positive control (Mitomycin C injected i.p. at 4 mg/kg two times for a total dose of 8 mg/kg).
Year : 1981
GLP : Yes
Test substance : Zirconium octoate (24%), [Zirconium 2-ethylhexanoate (24%)], batch #Z8702; specific gravity 1.24; miscible in corn oil.
Method :
Method detail : Preliminary toxicity study was used to select upper dose for micronucleus test. Animals (18 – 21 g) fasted overnight and orally dosed (two doses, 24 hours apart). Standard volume per dose was 0.1 mL/10 g body weight. At the highest dose, pilo-erection, hypopnea, ptosis, lethargy, and pale external extremities were observed one-half hour after dosing. Two deaths occurred in this group. At the end of 30 hours, all animals were sacrificed. Femurs were cleared and one epiphysis removed from each bone; a bone marrow smear was made onto a slide containing calf serum, cleaned in methanol for 24 hours, air dried, fixed in methanol overnight, air dried, placed in buffer distilled water and stained with Giemsa. The number of micronucleated cells per 1000 polychromatic erythrocytes per animal and the rate of normochromatic to polychromatic erythrocytes was determined. Comparisons to control were made using Wilcoxon's Sum of Ranks test at $p > 0.10$.
Result : No evidence of mutagenic potential was found. Test material groups produced micronucleated cell counts comparable to the vehicle control and to historical controls (0.1 – 1.8). Positive control response indicated a mean of 60.6 micronucleated cells per 1000 polychromatic erythrocytes. Ratio of normochromatic to polychromatic erythrocytes was comparable in test material and vehicle control groups (1.6). The positive control gave an increased ratio of 4.87.
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (Appendix B).
Metal: A single oral administration of an aqueous solution of zirconium oxychloride to mice of both sexes at concentrations from 220 to 2250 mg/kg induced chromosomal abnormalities in bone marrow cells, with the frequencies of aberration directly proportionate to the concentrations used. Zirconium oxychloride caused dose-dependent enhancement of the occurrence of chromosomal aberrations and sister chromatid exchanges in

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Reliability : human peripheral blood leucocytes. (Appendix C).
: (2) Reliable with restrictions. Comparable to guideline. Incomplete description of test material.

Reference : Richold, M., Richardson, J.C., and A. Howell, 1981. Micronucleus test on Zirconium Octoate 24% [Zirconium 2-ethylhexanoate (24%)], study conducted for Tenneco Chemicals, Inc. by Huntingdon Research Centre, Huntingdon, England.

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (Appendix B). In the most reliable study (Studies E and F, Appendix B), the NOEL for teratogenic and developmental effects in rats was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-

toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(Appendix B, Studies E & F).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:

Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid (as sodium 2-ethylhexanoate). Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant

increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

This study did not provide information on water consumption, concentration of test substance in drinking water, or incidence of effect within animal or litter. There was no analysis of dosing solutions. No criteria were provided to indicate how many abnormal sperm were required for a positive response. All animals were naïve and not proven breeders, so reduced mating success may not be treatment-related. No confirmation of estrous cycle; no data on effect of the test substance on gestation period. Thus, the apparent effect on physical development of pups from the high-dose group may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals within a group to be a reliable indicator of male function. (Appendix B).

Reliability :
Reference :

6.0 OTHER INFORMATION

Long term exposure to zirconium may enhance the humoral immune response and induce a state of hypersensitivity, based upon an enhanced response of immunoglobulin-M (IgM) antibody production in mice intraperitoneally injected with zirconium oxychloride at low doses. (Appendix C).

6.1 CARCINOGENICITY

Zirconium sulfate was administered at a level of 5 ppm in drinking water in lifetime studies in rats. The diet contained an additional 2.66 ppm of an unknown Zr moiety. No evidence was found of any biological or toxicological activity of zirconium, except to affect inconsistently the body weight of older animals. There was also no evidence that zirconium was tumorigenic in a rat strain (Long-Evans) with appreciable (20%) tumor incidence. (Appendix C).